Current Management of Small Cell Lung Cancer

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KEYWORDS

• Small cell lung cancer • Limited stage • Advanced stage • Chemotherapy

In 2010, approximately 222,000 cases of lung and bronchus cancers were anticipated to be diagnosed in the United States,[1] and worldwide, lung cancer is the eighth most common cause of death, killing an estimated 1.3 million people in 2004.[2] Small cell lung cancer (SCLC) is a high-grade, neuroendocrine carcinoma of the lung, named for its histologically distinct features, including small cells with sparse cytoplasm, fine chromatin, nuclear molding, and the presence of markers of neuroendocrine differentiation such as synaptophysin and chromogranin A. In the United States, SCLC accounts for a shrinking percentage of lung cancers, from 17% in 1986 to 13% in 2002, with non–small cell lung cancer (NSCLC) making up most of the remaining fraction.[3] This decreasing incidence may be a result of recent advances in public health measures, such as antismoking campaigns and bans on smoking in the workplace and other public places.[4] Because improvements in survival among patients with SCLC have been only modest over the last 30 years, the best way to eliminate morbidity from this disease may be through prevention.[3]

CLINICAL PRESENTATION AND STAGING

Presenting symptoms of SCLC are usually related to the tumor burden or effects of metastatic disease burden. Most disease presents in the central airways and mediastinum, leading to cough, shortness of breath, chest pain, hemoptysis, and compression of the superior vena cava. Common manifestations of metastatic disease include fatigue, anorexia, weight loss, headaches, and neurologic symptoms, with less than 10% of patients being asymptomatic at the time of presentation.[5] SCLC also has a propensity to cause paraneoplastic syndromes in up to 40% of patients as a result of release of peptide hormones. These syndromes include hyponatremia from inappropriate antidiuretic hormone secretion and Cushing syndrome from tumor-derived adrenocorticotropic hormone production. Less frequently, antigenic similarity to nervous system proteins triggers inappropriate autoimmune reactions, leading to neuromuscular disorders such as proximal motor weakness from Lambert-Eaton myasthenic syndrome, encephalomyelitis from anti-Hu antibodies, or cerebellar degeneration from anti-Purkinje cell antibodies.[6] Although the hormone-mediated paraneoplastic syndromes often respond to effective anticancer therapy, the antibody-mediated neurologic disorders often persist even despite disease response.

Although the *American Joint Commission on Cancer, Seventh Edition* staging criteria include both NSCLC and SCLC,[7] in clinical practice few SCLCs are diagnosed as small, peripheral solitary nodules with lymph nodes isolated to the lung

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(stage I–IIB). In contrast, the 2-stage Veterans Administration Lung Study Group staging system is a useful and simple staging system. Limited stage (LS) is disease contained within 1 hemithorax, including the primary tumor, mediastinal nodes, and ipsilateral supraclavicular disease. Extensive stage (ES) is disease that cannot be contained in a single radiotherapy portal, including overtly metastatic disease. Historically the staging workup included computed tomography (CT) scan of the torso, bone scan, brain magnetic resonance imaging or CT with contrast, and occasionally a bone marrow biopsy. [^{18}F]fluorodeoxyglucose positron emission tomography/CT scans are sufficiently sensitive to replace the bone scan and biopsy, but cannot substitute for dedicated brain imaging. With modern staging tools, the proportion of patients diagnosed with ES-SCLC has increased from 50% to 75% over the last 30 years, but the prognosis of patients has changed minimally. The median overall survival (OS) in LS disease is approximately 20 months, with expected 5-year survival less than 15%. In ES disease the expected median survival is only 8 to 12 months, and less than 2% of patients survive past 5 years.[4] Therefore, it is hoped that ongoing clinical research will yield important advances in the treatment of SCLC.

STANDARD TREATMENT OF SCLC

The treatment of LS-SCLC involves multimodality therapy with concurrent thoracic radiotherapy and chemotherapy with cisplatin and etoposide,[8] based on a meta-analysis that showed a 14% reduction in the mortality of LS patients treated with radiotherapy in addition to chemotherapy.[9] Some treatment paradigms that have incrementally improved on this backbone of concurrent chemoradiation include the commencement of radiotherapy early in the course of treatment, consideration of twice-daily thoracic radiation over a shorter total course, and the use of prophylactic cranial irradiation (PCI) in selected patients. Addressing the optimal timing of initiation of radiation, a meta-analysis published in 2007 reported a significant OS benefit when radiotherapy started within 9 weeks of chemotherapy or before the third cycle of chemotherapy, particularly in patients who received hypofractionated (twice-daily) courses of radiation.[10] One commonly used schedule is twice-daily thoracic radiation given in 1.5-Gy fractions to 45 Gy over 3 weeks, based on a study among 419 patients that showed an improvement in median survival from 19 months to 23 months among patients receiving the accelerated course.[11] However, 1 criticism is that 45 Gy may be an inadequate dose of radiation, compared with the more typical 60 to 70 Gy. To help address this question, another trial used a treatment break midway through in the hypofractionated arm to try to make the biologic effective doses more similar, and did not report a survival difference between the groups.[12] Therefore, the adoption of twice-daily radiotherapy in LS-SCLC has been limited. To provide more conclusive evidence regarding the best radiotherapy approach, an ongoing 3-arm intergroup trial randomizes patients to twice-daily standard radiation to 45 Gy, daily radiation to 70 Gy, or a hybrid of the 2 techniques (NCT00632853).

After completion of chemoradiotherapy, PCI should be considered in patients with systemic disease control and no evidence of metastases on repeat cranial imaging. A meta-analysis included 987 patients and reported a 5% absolute increase in the rate of 3-year survival in patients who received PCI as well as a decrease in the risk of brain metastases.[13] Doses of radiation used for PCI are generally lower than full treatment doses in patients with known brain metastases.

Although the single prospective randomized clinical trial that evaluated the role of surgery in SCLC reported no benefit for resection in patients who achieved a response to chemotherapy,[14] a recent retrospective review showed impressive 1-year and 5-year survival times of 75% and 50% among 59 patients who had undergone complete surgical resection.[15] Surgery seems to be most appropriately restricted to patients presenting with extremely limited disease (ie, clinical stage I by the American Joint Commission on Cancer criteria). Adjuvant chemotherapy and PCI should be considered in all patients who undergo surgical resection.

The standard treatment of ES-SCLC consists of chemotherapy alone, generally cisplatin or carboplatin plus etoposide for up to 6 cycles, followed by watchful waiting.[16] Even patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4 as a result of disease should be considered for treatment with chemotherapy, because response rates to chemotherapy exceed 75% and clinical improvement can be observed within a few days. After initial chemotherapy, PCI is recommended, as in LS disease, as a result of an improvement in 1-year OS of 15%.[17] However, mounting evidence suggests that PCI increases the chances of hair loss, fatigue, and cognitive impairment, and therefore may hinder quality of life in patients.[18] Despite rapid and impressive responses to initial chemotherapy, virtually all patients eventually relapse. The choice of subsequent treatment depends on the duration and magnitude of response to platinum-based chemotherapy. Patients with an initial response to

treatment lasting more than 3 months from the completion of chemotherapy are considered chemotherapy sensitive. These patients have about a 25% chance of response to second-line treatment, in contrast with patients without an initial response or earlier relapse, who are considered refractory to chemotherapy and have a less than 10% chance of response. In patients with disease control for 12 months or more from the time of initial treatment, a second course of a platinum/etoposide regimen often can achieve disease control, although for a more limited period. Otherwise, salvage chemotherapy generally consists of nonplatinum single-agent chemotherapy drugs; agents with efficacy in SCLC include camptothecins, taxanes, and gemcitabine. In the United States, topotecan is approved for the treatment of patients based on a phase III trial that showed a 25% response rate and more symptomatic improvement compared with a more toxic regimen of cyclophosphamide, doxorubicin, and vincristine.[19] An oral version of topotecan has also been approved with similar efficacy.[20,21] Other single agents can be used sequentially, with diminishing response rates and duration of response depending on the line of therapy, with few patients achieving disease control after the third line of treatment.[15,16] Therefore, most clinical trials of novel therapies are initially designed for patients with ES disease, with the goal that active drugs could be subsequently tested in the LS setting. The remainder of this article focuses on phase II and III clinical trials involving novel chemotherapeutics and targeted therapies in ES-SCLC.

RECENT CLINICAL TRIALS INVOLVING CHEMOTHERAPY

Irinotecan

Several older trials investigated alternatives to platinum plus etoposide, but failed to show superiority. For example, even although gemcitabine has single-agent activity in relapsed, refractory, and resistant SCLC,[22,23] carboplatin plus gemcitabine showed no additional efficacy over cisplatin/etoposide.[24] Similarly, phase III trials involving the addition of a third drug, including ifosfamide, epirubicin, or paclitaxel, to cisplatin and etoposide have all reported increased toxicity but no survival benefit.[25–27] However, a camptothecin, irinotecan, did show early promise as a replacement for etoposide in first-line treatment of ES-SCLC (**Table 1**).

A phase II study initially suggested activity of the topoisomerase I inhibitor topotecan, with response rates of 38% in sensitive patients and 6% in refractory patients,[28] and topotecan is approved for use in the United States in recurrent SCLC. Based on this finding, the related agent irinotecan was paired with platinum agents in the frontline setting. In Japan, a phase III study in 2002 compared cisplatin/etoposide treatment with cisplatin and irinotecan. This study was terminated early because of an improvement in median OS in patients receiving irinotecan (60 mg/m^2 irinotecan given on days 1, 8, and 15 of a 3-week cycle) (12.8 months) compared with patients receiving etoposide (9.4 months).[29] Although this regimen was adopted as standard of care in Japan, concern remained that these results may not be applicable to Western countries. Therefore, 3 subsequent phase III studies were conducted using similar regimens. In the first, a modified dosing schedule of irinotecan (65 mg/m^2) was used, giving drug on days 1 and 8 of a 3-week cycle. Among 331 patients randomized in a 1:2 fashion to etoposide or irinotecan, no survival difference was observed, with 9.3 months on irinotecan and 10.2 months on etoposide. Another phase III trial was conducted with the same irinotecan dosing as in the Japanese study.[30] Among 651 patients, this trial also showed no difference in survival (9.9 months for irinotecan and 9.1 months for etoposide, $P = .71$), with more diarrhea on the irinotecan arm and more hematological toxicity on the etoposide arm. In a third trial, the more commonly used platinum chemotherapeutic carboplatin (area under the curve of 5 mg-min/mL) was combined with irinotecan (50 mg/m^2) on days 1, 8, and 15, and these were compared with carboplatin and etoposide. Of 216 evaluable patients, median survival was 10 months among patients receiving irinotecan and 9 months among patients receiving etoposide.[31] Platinum plus irinotecan is an acceptable alternative to platinum plus etoposide in the first-line treatment of ES-SCLC, but superiority and impressive median survival time of more than 12 months were not replicated in 3 subsequent Western trials.

Amrubicin

Amrubicin is a novel anthracycline derivative with antitumor activity based on inhibition of DNA topoisomerase II.[32] In contrast to the related compound doxorubicin, amrubicin has not been associated with cumulative cardiotoxicity in animal models or in subsequent human studies, but does have neutropenia as a dose-limiting toxicity.[33,34] Amrubicin has been approved in Japan for use in SCLC and NSCLC since 2006 based on promising phase II studies.[35] As a single agent in the first-line setting, amrubicin had a 75% response rate among 35 previously untreated patients,[36] and had an 89% response rate in combination with carboplatin in an elderly population.[37] A more recent study in

Table 1
Recent randomized clinical trials of chemotherapy in SCLC

Trial and Population	Agents	Patients (n)	Response Rate (%)	PFS (mo)	OS (mo)
JCOG 9511[29]	Cisplatin/**irinotecan**	75	84[a]	6.9[a]	12.8[a]
First-line	Cisplatin/etoposide	77	68	4.8	9.4
Hanna et al[86]	Cisplatin/**irinotecan**	221	48	4.1	9.3
First-line	Cisplatin/etoposide	110	44	4.6	10.2
SWOG S0124[30]	Cisplatin/**irinotecan**	324	60	5.8	9.9
First-line	Cisplatin/etoposide	327	57	5.2	9.1
Schmittel et al[31]	Carboplatin/**irinotecan**	106	54	6.0	10.0
First-line	Carboplatin/etoposide	110	52	6.0	9.0
North Japan 0402[41]	**Amrubicin**	29	38[a]	3.5	8.1
Relapsed/refractory	Topotecan	30	13	2.2	8.4
Jotte et al[45]	**Amrubicin**	50	44[a]	4.5	9.2
Relapsed/refractory, chemosensitive	Topotecan	26	15	3.3	7.6
SPEAR[51]	**Picoplatin**	268	4	2.1[a]	4.8
Refractory or resistant second-line	Best supportive care	133	0	1.5	4.6
GALES (Global Analysis of Pemetrexed in SCLC)[56]	Carboplatin/ **pemetrexed**	453	31	3.8	8.1
First-line	Carboplatin/etoposide	455	52[a]	5.4[a]	10.6[a]
ACT-1[46]	**Amrubicin**	424	31[a]	4.1	7.5
Sensitive or refractory second-line	Topotecan	213	17	4.0	7.8

Boldface type, investigational agent.
[a] Statistically superior value in comparison with opposite arm, $P<.05$.

Table 2
Recent randomized clinical trials of antiangiogenic therapies in SCLC

Trial and Population	Agents	Patients (n)	Response Rate (%)	PFS (mo)	OS (mo)
Pujol et al[62]	Thalidomide	49	N/A	6.6	11.7
First-line with chemo, delayed start	Placebo	43	N/A	6.4	8.7
Lee et al[63]	Carboplatin/ etoposide/ thalidomide	177	80	7.6[a]	12.1
First-line LS	Carboplatin/ etoposide/placebo	191	76	7.6[a]	13.1
Lee et al[63]	Carboplatin/ etoposide/ thalidomide	188	68	7.6[a]	8.0[b]
First-line ES	Carboplatin/ etoposide/placebo	168	80	7.6[a]	9.1
SALUTE[70]	Platinum/etoposide/ bevacizumab	50	48	5.5[b]	9.4
First-line	Platinum/etoposide/ placebo	52	58	4.4	10.9

Abbreviation: N/A, not applicable (performed in patients selected for initial response).
[a] For combined LS and ES-SCLC groups; PFS not reported by stage.
[b] Statistically superior value with $P<.05$.

elderly patients was terminated early because of a 10% higher treatment-related death rate in the amrubicin arm, compared with carboplatin/etoposide, although there were no statistically significant differences between the 2 arms with respect to response, progression, survival, or quality of life.[38] The West Japan Thoracic Oncology Group investigated adding 3 cycles of amrubicin sequentially after 3 cycles of cisplatin and irinotecan in a single-arm phase II study, finding an overall response rate of 79% with 1 complete response among 45 patients. Median PFS was 6.5 months and OS was 15.4 months. Only 64% of patients were able to complete the entire planned course of treatment, with myelosuppression as the dominant toxicity.[39]

However, most development of amrubicin has been as a second-line agent. A phase II study of second-line use of amrubicin by the Thoracic Oncology Research Group in Japan (study 0301) showed a response rate of 52% among 44 platinum-sensitive patients and a 50% response rate among 16 platinum-refractory patients.[40] The North Japan Lung Cancer Study Group 0402 Trial randomized 60 patients (36 sensitive and 23 refractory) to amrubicin or topotecan as second-line treatment, with response rates of 38% in the amrubicin arm versus 13% for topotecan.[41] Recent single-arm phase II trials in Japan also piloted amrubicin in combination with other chemotherapy in the relapsed setting, and showed a 58% response rate using amrubicin plus carboplatin,[42] and a 43% response rate using amrubicin plus topotecan.[43] In a Western population, 75 patients with platinum-refractory SCLC were treated in a single-arm phase II study with amrubicin, with a lower response rate of 21% and a median OS of 6.0 months.[44] However, in a subsequent randomized phase II study in the United States comparing amrubicin with topotecan in 76 chemosensitive relapsed patients, results were closer to the Japanese data, with significantly higher response rate for amrubicin (44% vs 15%, $P = .21$), and trend toward better progression-free survival (PFS) (4.5 vs 3.3 months) and OS (9.2 vs 7.6 months).[45] Results of the international phase III ACT-1 trial were recently reported, in which 637 patients with sensitive or refractory SCLC were randomized in a 2:1 fashion to amrubicin versus topotecan.[46] Unfortunately, for amrubicin as compared with topotecan, there was an increase in response rate (31% vs 17%) but no difference in PFS (4.1 vs 4.0 months) or overall survival (7.5 vs 7.8 months). There was a trend toward an overall survival benefit among the 295 patients with refractory disease (6.2 vs 5.7 mo, HR 0.77, p = 0.047), but this small 15 day improvement may not be a clinically relevant difference. The future of this agent, which had received FDA "fast track" status in 2008, is uncertain at present.

Picoplatin

Picoplatin is an analogue of cisplatin that includes a large picoline ring intended to reduce susceptibility to certain mechanisms of platinum resistance.[47] Myelosuppression is the dose-limiting toxicity, with thrombocytopenia more common than neutropenia. Ototoxicity and nephrotoxicity are infrequent.[48] In a single-arm phase II trial of 37 patients, a response rate of 15% was observed among platinum-resistant patients and 8% among platinum-sensitive patients, with survival of 6.3 and 8.2 months, respectively.[49] In another trial of relapsed and refractory patients, treatment with picoplatin produced just a 4% response rate, although the disease control rate was 43% and median survival was 6.3 months.[50] Results were recently reported from the phase III SPEAR (Study of Picoplatin Efficacy After Relapse) trial, which randomized 401 relapsed or refractory patients to picoplatin or best supportive care.[51] The median survival time was similar between the groups: 4.8 months for picoplatin versus 4.6 months for BSC. However, a subgroup analysis revealed a modest survival advantage among platinum-refractory patients, with a significantly different median survival time of 4.9 months versus 4.3 months. Given the small magnitude of this difference and the failure to show improvement in OS, further development of picoplatin in SCLC is unlikely.

Pemetrexed

Pemetrexed is a multitargeted antimetabolite chemotherapy that inhibits essential enzymes for tumor nucleotide metabolism such as thymidylate synthase.[52] Pemetrexed has been shown to be effective and well tolerated in the treatment of NSCLC of adenocarcinoma histology.[53,54] In SCLC, a phase II study reported that the combination of pemetrexed with either cisplatin or carboplatin appeared tolerable, with a median OS of 10.4 months.[55] Based on this finding, a randomized phase III trial was conducted to compare carboplatin/etoposide with carboplatin/pemetrexed. An interim safety analysis halted enrollment halfway through because of inferior survival in the pemetrexed arm. Among 453 patients treated with carboplatin and pemetrexed, the response rate was 31% and OS was 8.1 months, compared with response rate of 52% and OS of 10.6 months in the carboplatin/etoposide arm.[56]

Even in relapsed or refractory patients, pemetrexed has minimal activity, with a response rate of less than 1%.[57] This situation may be because

of the relatively higher expression of 1 target of pemetrexed, thymidylate synthase, compared with either the adenocarcinoma or squamous histologic subtypes of NSCLC.[58] Given the potential inferiority, the use of pemetrexed in SCLC is not recommended outside the scope of a clinical trial.

TARGETED THERAPIES

Thalidomide

Thalidomide is a small molecule with antitumor activity that may result from antiangiogenic effects, thereby depriving solid tumors of a blood supply.[59] In ES-SCLC, thalidomide has been tested in the frontline setting in several clinical trials. In a small phase II trial, thalidomide with carboplatin and etoposide yielded a response rate of 68%, with PFS of 8.1 months and median OS of 10.1 months and appeared to be safe.[60] A second phase II trial of a different design used maintenance thalidomide immediately after first-line chemotherapy. Although response rates were not meaningful in this study, the median OS was 12.8 months (**Table 2**).[61]

Based on these promising results and demonstration of tolerability, there were 2 randomized trials. One trial used a French backbone of cisplatin, etoposide, cyclophosphamide, and epirubicin for 2 cycles, followed by continuation of chemotherapy with the addition of thalidomide, 400 mg daily, or placebo.[62] In this relatively small trial of 92 patients, those who received thalidomide had a numerically better, but not statistically significant, median OS of 11.7 months compared with 8.7 months among patients treated with placebo ($P = .16$). To confirm this trend in a larger setting, another trial randomized 724 patients with both ES-SCLC and LS-SCLC to thalidomide (200 mg daily) or placebo.[63] This study showed no survival difference between the treatment groups with LS disease, but among patients with ES-SCLC, the median OS was significantly worse in patients treated with thalidomide (8.0 months) compared with patients treated with placebo (9.1 months). The patients treated with thalidomide had almost a 20% incidence of thrombotic events, including deep venous thrombosis and pulmonary embolism, compared with 10% in the placebo group, suggesting this difference in survival may have been related to side effects. Thalidomide was also associated with a higher incidence of grade 3 or 4 neuropathy in this trial, leading to the conclusion that thalidomide should be avoided in the treatment of SCLC.

Antiangiogenesis Agents: Bevacizumab

Treatment with bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), results in deprivation of a growth factor that is necessary to support the growth of macroscopic tumors.[64] In NSCLC, the addition of bevacizumab to carboplatin and paclitaxel improves OS.[65] In SCLC, the ECOG 3501 single-arm phase II trial tested the addition of bevacizumab to cisplatin/etoposide in 63 patients, with a response rate of 63%, PFS of 4.7 months, and median OS of 10.9 months. One patient experienced a grade 3 pulmonary hemorrhage.[66] Two single-arm phase II trials also were conducted combining bevacizumab with platinum and irinotecan. One used carboplatin in the combination with a response rate of 84%, a median PFS of 9.1 months, and a median OS of 12.1 months,[67] whereas a larger study using cisplatin showed a response rate of 75%, a median PFS of 7.1 months, and median OS of 11.7 months.[68] Bevacizumab was also incorporated into the treatment of LS-SCLC in combination with radiation and carboplatin/irinotecan-based chemotherapy. Among 29 treated patients, 2 developed tracheoesophageal fistulae, 1 fatal, and a third patient died of aerodigestive hemorrhage, prompting early closure of the study and a recommendation to avoid bevacizumab in the setting of concurrent radiotherapy.[69] However, randomized clinical trials have been conducted only with the platinum/etoposide backbone. In the SALUTE (Study of Bevacizumab in Previously Untreated Extensive-Stage Small-Cell Lung Cancer) phase II trial, 102 patients were randomized to 4 cycles of treatment with carboplatin or cisplatin and etoposide, with and without bevacizumab. In a preliminary report of this trial, patients who received bevacizumab had a significantly better PFS (5.5 months vs 4.4 months without bevacizumab).[70] However, patients who received chemotherapy plus bevacizumab had no difference in OS (9.4 months) compared with patients who received chemotherapy plus placebo (10.9 months). Based on this finding, there are no reported plans for a phase III trial randomized trial of bevacizumab in SCLC.

Antiangiogenic Tyrosine Kinase Inhibitors

Sorafenib, a small molecule tyrosine kinase inhibitor, has antiangiogenic and antiproliferative properties based on its ability to inhibit B-raf and the VEGF receptors VEGFR1, 2, and 3. Sorafenib has been tested in several different solid tumors and has proven efficacy in renal cell carcinoma and hepatocellular carcinoma.[71,72] Toxicities typically include fatigue, rash, hand-foot syndrome, and gastrointestinal disorders. This drug seems to have modest activity in SCLC, as shown by a phase II trial.[73] Among 38 patients with platinum-sensitive

disease, 4 partial responses were seen (11% response rate), with PFS of 2.2 months and OS of 5.3 months. Among 45 patients with platinum-refractory disease, the response rate was 2%, with PFS of 2.0 months and OS of 6.7 months. Although this study did not show sufficient signal to further pursue development of single-agent sorafenib in SCLC, a phase I/II trial is ongoing in combination with chemotherapy (NCT00726986).

Sunitinib is another tyrosine kinase inhibitor that inhibits the VEGFR, platelet-derived growth factor (PDGF) receptor, and the KIT receptors. Two frontline clinical trials are currently in the enrollment phase, including a randomized phase II cooperative group study in combination with platinum/etoposide (NCT00453154), and a trial in patients with stable disease as a maintenance agent after initial chemotherapy (NCT00616109). A phase II study is also being conducted with the related VEGFR, PDGF, and c-kit inhibitor, pazopanib, in patients with relapsed or refractory disease (NCT01253369). These phase II studies will ideally help to define the role of VEGF inhibitors in the treatment of SCLC.

Other Agents

As the molecular pathways leading to tumorigenesis in SCLC have been elucidated, efforts have been made to incorporate targeted agents into clinical trials. Some specific pathways of interest include apoptosis, the mTOR (mammalian target of rapamycin) signaling pathway, and the hedgehog (Hh) signaling pathway as possible targets.

Avoidance of normal programmed cell death (apoptosis) is 1 mechanism of resistance to chemotherapy, and the Bcl-2 protein seems to mediate resistance to chemotherapy-induced apoptosis in many SCLCs.[74] Navitoclax (ABT-263) is a small molecule that acts as a BH3 mimetic, thereby lowering the cellular threshold for apoptosis by inhibiting Bcl-2. In a phase I safety study, including 29 patients with relapsed or refractory SCLC and pulmonary carcinoid, 8 patients had stable disease and 1 patient with SCLC had a response that lasted 2 years.[75] Up to 40% of patients experienced diarrhea, nausea, vomiting, and fatigue. With some evidence of activity in this study, ongoing development includes a trial to investigate the safety of the combination of navitoclax together with cisplatin and etoposide (NCT00878449).

An alternative, but unproductive strategy that was attempted to target Bcl-2 was the antisense oligonucleotide, oblimersen, which appeared safe in combination with chemotherapy in phase I studies.[76] However, in a small randomized phase II study of 56 patients, survival was worse in patients receiving oblimersen compared with placebo with carboplatin and etoposide, suggesting that further development will not take place.[77]

The mTOR and PI3K/AKT kinase signaling pathways are also active in many malignancies and regulate processes from cellular proliferation to control of apoptosis. Everolimus is a rapamycin derivative that inhibits mTOR that is approved by the US Food and Drug Administration for treatment of advanced kidney cancer. In SCLC, an early report of a phase II trial showed some activity in patients with relapsed and refractory disease. Among 35 evaluable patients, there was 1 patient who responded and 8 patients with stable disease, with median PFS of 1.4 months and median OS of 5.5 months.[78] There is an ongoing frontline clinical trial with everolimus in combination with carboplatin and etoposide (NCT00466466); based on the final results from these studies further development will be determined.

The Hh signaling pathway is critical for normal growth and development, and many lung cancer cell lines are dependent on this pathway for survival.[79] Hh signaling may be critical for the survival and self-renewal of a small number of cancer stem cells, which are often resistant to chemotherapy and may be responsible for tumor resistance in SCLC.[80] Derivatives of a naturally occurring inhibitor of this pathway, cyclopamine, have elicited remarkable responses in patients with metastatic basal cell cancer and medulloblastoma.[81,82] In SCLC, an ongoing cooperative group clinical trial, ECOG 1508, is a first-line study with cisplatin and etoposide, in combination with either the Hh inhibitor GDC0449 or the insulinlike growth factor 1 receptor (IGF-1R) antibody cixutumumab (NCT00887159). The addition of the IGF-1R antibody based on preclinical evidence inhibition of this pathway may potentiate chemotherapy, epidermal growth factor receptor inhibitors, and even radiation effects in lung cancer cell lines.[83–85] This trial may show whether inhibitors of either of these pathways have activity in SCLC.

SUMMARY

Despite numerous clinical trials and excellent responses to first-line chemotherapy, there have been few substantial clinical advances in the treatment of ES SCLC over the last 30 years. Irinotecan is an active agent both in combination with platinum agents and in the second-line setting, but pemetrexed and picoplatin seem to be relatively ineffective. The novel anthracycline amrubicin showed early promise in small clinical trials, but unfortunately was not superior to topotecan.

Inhibitors of angiogenesis, although conceptually promising, have not yielded additional clinical benefit. It is hoped that future advances in the biology of the disease will lead to the development of effective targeted therapies.

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